REMARKS

Claims 1, 9, 11-14, and 15-18 have been amended. New claim 31 has been added. Support for the amendments and new claim can be found at page 3, lines 16-20, page 4, lines 3-7, page 20, lines 12-17, and page 21, lines 3-5 of the specification; at column 32, lines 13-27 of U.S. Pat. No. 5,736,137; and at page 45, line 17 through page 46, line 5, and page 60, lines 8-14, of WO 00/75348. Both of these documents were expressly incorporated by reference at page 21, lines 15-17; page 27, lines 16-17; and page 44, lines 24-25 of the present specification at the time of filing. Claims 19-30 have been withdrawn by the Examiner as directed to a non-elected species. Therefore, claims 1-31 are pending in the application. Entry of the Amendment and reconsideration of the claims in view of the following Remarks is respectfully requested.

Specification

The specification has been amended as required by the Examiner to: 1) provide reference to priority application USSN 60/280,805; 2) replace the title of the invention with a more descriptive title; and 3) correct typographical errors and insert trademark symbols where appropriate. The specification has also been amended to include certain portions of two documents expressly incorporated by the specification, as discussed above.

35 U.S.C. § 112, first and second paragraphs

Claims 11, 12, 15, and 18 were rejected under 35 U.S.C. 112, first paragraph, for lack of enablement. The Examiner asserts that "S2C6" and "C2B8" antibodies are required to practice the claimed invention. Claims 11, 12, 15, and 18 were also rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Although paragraph 8 of the Office Action also refers to claims 35-38, it is Applicants' understanding that the reference to these claims was inadvertent since only claims 1-30 were pending in the application. The Examiner contends that the recitation of "S2C6" and "C2B8" antibodies is indefinite because their characteristics are unknown. Applicants traverse these rejections.

Applicants note that page 21, lines 15-17 of the specification expressly incorporates by reference U.S. Pat. No. 5,736,137. Applicants submit this document discloses the identity and characteristics of C2B8 and methods for its production.

Additionally, the amended claims recite that "C2B8" is rituxumab (e.g., RITUXAN®). Applicants submit it is well-known that RITUXAN® is commercially available, and therefore is readily accessible to the public.

The amended claims also recite that S2C6 comprises the V_L amino acid sequences of SEQ ID NO:1 and SEQ ID NO:2 and the V_H amino acid sequences of SEQ ID NO:6 and SEQ ID NO:7 of the incorporated reference WO 00/75348. Applicants submit this reference discloses S2C6 and methods for its production, and that S2C6 is readily obtainable using these methods.

For the foregoing reasons, withdrawal of these rejections is respectfully requested.

35 U.S.C. § 102

Claims 1-18 were rejected under 35 U.S.C. § 102(e) as anticipated by Hanna et al. (US 2001/0018041 A1). The Applicants traverse this rejection.

The present claims are directed to methods for the treatment of a neoplastic disease or disorder characterized by cells expressing CD40 in a mammal, comprising administering to the mammal a therapeutically effective amount of a CD40 agonist in combination with a CD20 binding agent.

As an initial matter, Applicants note that "[a] claim is anticipated only if each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference." *MPEP 2131* (quoting *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)).

Applicants submit that Hanna et al. does not disclose each and every element of the present claims. Specifically, Hanna et al. does not disclose a method comprising the use of a CD40 agonist in combination with a CD20 binding agent. Rather, Hanna et al. discloses methods of treating B-cell lymphomas and leukemias with the combination of anti-CD20 antibodies and "an anti-CD40L antibody or other CD40L antagonist" (see Abstract and paragraph 37; emphases added). Hanna et al. discloses that a "CD40L antagonist" is a molecule that interferes "with the interaction of CD40L and its binding partner, CD40" (see paragraph 37). Applicants submit that one of ordinary skill in the art would recognize that the "CD40L antagonist" disclosed by Hanna et al. is not a "CD40 agonist," as required by the present claims.

Consequently, claims 1-18 are patentable over Hanna et al. for at least this reason. Withdrawal of the rejection is respectfully requested.

35 U.S.C. § 103(a)

Claims 1-18 were rejected under 35 U.S.C. § 103(a) as unpatentable over Hanna et al. (US 2001/0018041 A1) in view of Siegall et al. (U.S. Patent No. 6,843,989) and Grillo-Lopez et al. (U.S. Patent No. 6,455,043).

The claims are directed to methods for the treatment of a neoplastic disease or disorder characterized by cells expressing CD40 in a mammal, comprising administering to the mammal a therapeutically effective amount of a CD40 agonist in combination with a CD20 binding agent.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met, namely: (1) the references must teach or suggest all of the claim limitations; (2) there must be a suggestion or motivation, either in the references or in the knowledge generally available to one of skill in the art, to modify the references to have all of the claim limitations; and (3) there must be a reasonable expectation of success. Applicants submit that not all of these requirements have been met, because the references do not suggest all of the claim limitations, there is no suggestion or motivation to combine or modify the references to disclose all of the claim limitations, and because there is no reasonable expectation of success.

As discussed above regarding the 35 U.S.C. 102 rejection, Hanna et al. does not disclose a method comprising the use of a CD40 agonist in combination with a CD20 binding agent. Rather, Hanna et al. discloses methods of treating B-cell lymphomas and leukemias with the combination of anti-CD20 antibodies and CD40L antagonists (see Abstract and paragraph 37). Applicants submit that the "CD40L antagonist" disclosed by Hanna et al. is not a CD40 agonist, as required by the present claims.

The addition of Grillo-Lopez et al. does not remedy the deficiencies of Hanna et al. Grillo-Lopez et al. is directed to the treatment of tumors with anti-CD20 antibodies (see Abstract). This reference does not discuss CD40 agonists, nor does it teach or suggest any advantage to combining a CD40 agonist with a CD20 binding agent for the treatment of tumors, or for any other reason.

Nor does Siegall et al. remedy the deficiencies of Hanna et al. or Grillo-Lopez et al. Siegall et al. discloses methods of treating cancers by administering a CD40 binding protein that potentiates the binding of CD40 to CD40 ligand (see Abstract), but does not teach or suggest combining CD40 agonists with CD20 binding agents as required by the claims, whether for the treatment of cancer or for any other reason.

Moreover, Applicants submit that one of ordinary skill in the art would not be motivated to modify the method of Hanna et al. to obtain a combination therapy that comprises administering a CD20 binding agent, such as taught by Grillo-Lopez et al., and the CD40 binding protein disclosed by Siegall et al. (that potentiates the binding of CD40 to CD40 ligand) as a substitute for of the CD40L antagonist disclosed by Hanna et al. (that interferes with the interaction of CD40L with CD40). Applicants note that in order to render the claims obvious, the prior art must suggest the desirability of modifying the teachings disclosed therein to obtain the claimed invention. *MPEP 2143.01I.* Applicants respectfully submit that no such suggestion is present in the cited art.

The Examiner's attention is directed to Example 3, where Hanna et al. discloses and exemplifies that the signaling produced by the interaction of CD40L and CD40 "prevents apoptosis of B-lymphoma cells by anti-CD20 antibody" (see title of Example 3). As shown in Table 1, Hanna et al. discloses that the presence of a CD40L antagonist *decreased* the ability of an anti-CD20 antibody (RITUXAN®) to mediate the killing of DHL-4 lymphoma cells by inducing apoptosis (see right-side column of Hanna et al. at page 13, lines 3-4). Hanna et al. concludes that combination therapies comprising the administration of anti-CD40L antagonists, such as IDEC-131, with an anti-CD20 antibody, such as Rituxan, would be "particularly useful" in treating certain CD40+ malignancies (see the prophetic Example 8 on page 14 of Hanna et al.).

Therefore, Applicants respectfully submit that Hanna et al. teaches away from substituting the anti-CD40L therapy taught by Hanna et al. with the therapy of promoting CD40/CD40L interactions taught by Siegall et al. As a result, combining Grillo-Lopez et al. with the teachings of Hanna et al. and Siegall et al. would not result in the presently claimed invention. One of ordinary skill in the art would conclude from reading Hanna et al. that it is desirable to interfere with the CD40/CD40L interaction by administering a CD40L antagonist in

order to enhance the ability of an anti-CD20 antibody to promote the killing of B-lymphoma cells via apoptosis. Consequently, one of ordinary skill would not have a reasonable expectation of success from Hanna et al. that combining a CD20 binding agent with a CD40 agonist, as recited by the present claims, would be beneficial in the treatment of a neoplastic disease or disorder.

Rather, it is the present specification that discloses that administering a combination of a CD20 binding agent with a CD40 agonist is useful in the treatment of neoplastic diseases or disorders, and results in anti-tumor activity that is superior to treatment with a CD20 binding agent alone or a CD40 agonist alone (see Example 1 and Figures 4-5 of the specification).

For at least the foregoing reasons, Applicants submit that claims 1-18 are patentable over Hanna et al., Grillo-Lopez et al., and Siegall et al., alone or in any combination. Withdrawal of the rejection is respectfully requested.

Summary

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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